Ophthalmol Ther
https://doi.org/10.1007/s40123-025-01164-5

ORIGINAL RESEARCH

Clinical Trial Simulation in Diabetic Retinopathy: Insights from Patients and Site Staff

Stela Vujosevic · Ivana Gunderson · Asma Burale · Ben Moody · Rebecca C. Stacy · Martin Gliem

Received: March 5, 2025 / Accepted: April 29, 2025

ABSTRACT

***Introduction*:** High patient burdens from diabetic retinopathy (DR)-associated vision loss and intravitreal therapy (IVT) support patient experience inclusion in DR trial designs. This trial simulation characterized patient and site staff opinions to improve future nonproliferative DR (NPDR) trial designs.

***Methods*:** Between March 27 and May 31, 2023, survey data were collected from trial simulation participants. After a preread and trial design animation, study features were simulated followed by a 75–90-min web-assisted telephone interview. Patients with NPDR and trial site staff from the United States, United Kingdom, and Germany were included. The likelihood of patient participation and the challenges faced by site staff in conducting the simulated clinical trial at their study site were assessed using a 1–7 scale. Outcomes were evaluated via thematic analysis and descriptive statistics.

***Results*:** Twenty-two patients aged 36–55 years and mostly female (59.1%), and 16 site staff were interviewed. Mean NPDR duration was 9.3 years; most patients (81.8%) had never participated in a clinical trial. Although eligibility criteria resembled other trials, site staff indicated that restrictive exclusion criteria of the trial simulation could limit recruitment and that endpoints did not match patients' goals, which mainly focused on saving vision. The proposed

Prior Presentation: This was presented at the 24th EURETINA congress in Barcelona, Spain, on September 19–22, 2024.

Supplementary Information The online version supplementary material available at https://doi.org/10.1007/s40123-025-01164-5.

S. Vujosevic (✉)
Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy
e-mail: stela.vujosevic@unimi.it

S. Vujosevic
Eye Clinic, IRCCS MultiMedica, Via San Vittore 12, 20123 Milan, Italy

I. Gunderson
Austin Clinical Research, Austin, TX, USA

A. Burale
Moorfields Eye Hospital NHS Foundation Trust, London, UK

B. Moody
London, UK

R. C. Stacy
Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA

M. Gliem
Boehringer Ingelheim International GmbH, Ingelheim, Germany

Published online: 08 July 2025

4–5-h on-site visits and 72-week trial length were considered "too long" by 45.5% and 50.0% of patients, respectively. For the 1:2 sham or active treatment allocation ratio, responses were 40.9% neutral, 36.4% positive, and 22.7% negative. Some patients misunderstood that sham injections imitate actual injections, expressing concerns about adverse events. Patients reported IVT-related anxieties, particularly IVT-inexperienced patients. Mean patient trial participation interest score was 4.9/7; 62.5% of site staff were interested in conducting the trial. Some proposed adaptations were implemented in the trial protocol (e.g., offering patient/caregiver transportation).

***Conclusions*:** Insights gained from respondent feedback in this simulation may inform future DR clinical trial design, potentially enhancing recruitment rates and patient experience.

PLAIN LANGUAGE SUMMARY

Diabetic retinopathy (DR) is an eye disease that is the major cause of blindness in working-age adults. The disease and its treatment involving injections into the eye may be burdensome and anxiety-inducing for patients. Given the challenges facing people with DR, when planning clinical trials, patients' points of view should be taken into account. This trial simulation study captured the views of patients, their caregivers, and clinical trial site staff from Germany, the UK, and the USA on designing and planning a phase 2 clinical trial in a type of DR called nonproliferative DR. Participants identified limitations with, and suggested potential improvements to, the clinical trial design. Limitations identified included the duration of the period where patients would have to stop treatment before the study, as there were concerns about disease progression. Many patients expressed confusion about the process for the imitation injection in the control group. The long trial duration and appointment times could potentially interfere with patients' responsibilities such as work and childcare, and the study outcomes did not align with patients' main priority of saving vision. Suggested changes to the study design were implemented, such as offering transport to the clinic for trial visits to help patients and caregivers to attend more easily. Despite these challenges, both patients and site staff expressed interest in participating in or conducting a trial similar to the simulated one. Considering these factors when designing future clinical trials may increase patient participation and create a positive view of clinical research.

Keywords: Clinical trial design; Clinical trial simulation; Nonproliferative diabetic retinopathy; Patient perspective; Telephone interview

Key Summary Points
Understanding how patients' views can enhance the clinical trial experience is important, particularly for people with diabetic retinopathy (DR) as the disease and its treatment, involving eye injections, are burdensome and anxiety-inducing for patients.
To better understand patients' views on improving the design and conduct of clinical trials in DR, we invited patients with nonproliferative DR from Germany, the UK, and the USA to participate in a trial simulation study; clinical trial site staff were also invited to participate.
Patient and site staff responses highlighted several ways trial designs could be improved, identified areas of trial design that were confusing for patients, and showed that patients and site staff were enthusiastic about participating in or conducting, respectively, a trial such as the one in the simulation.
The study highlighted logistical burdens for patients that should be taken into consideration and the importance of clearly explaining each aspect of trial treatments to patients.
Implementing these insights into future DR trial designs should improve the patient clinical trial participation experience, encouraging greater participation and enhancing the real-world applicability of trial results.

INTRODUCTION

There is growing acknowledgment of the value that patient voices can bring to ophthalmology [1, 2], including guiding research priorities and identifying outcome measures relevant to the patient experience [2]. Furthermore, guidance from the European Medicines Agency and United States Food and Drug Administration advises the inclusion of the patient voice as a key part of the clinical development process [3, 4]. Despite this, clinical trials rarely account for patient perspectives when considering trial design and conduct.

Ignoring the patient experience in clinical trial designs can lead to a range of issues with the resulting data, including but not limited to a lack of relevance to patient unmet needs, limited translation into real-world practice due to underrepresentation of some patient groups, use of endpoints that are not relevant for patients, and a greater number of dropouts from the trial [5, 6]. However, in some cases, the patient voice has been sought in clinical trial design through the performance of trial simulation studies. In these studies, patients are asked to review material that outlines the trial design and conduct and then provide feedback, which is then analyzed and incorporated into trial protocols. Similarly, the views of healthcare professionals (HCPs) and other clinical trial site staff can also be sought as additional perspectives [7–9].

Diabetic retinopathy (DR) is the leading cause of vision loss in adults of working age [10, 11], and a previous projection for 2020 estimated that approximately 3.2 million people worldwide are visually impaired as a result of DR [12]. The proportion of blindness and impairment that is due to DR has also increased over time [13]; therefore, there is an increasing need for effective treatment options to manage and prevent DR-associated vision loss. Current treatment for DR is a watch-and-wait approach in combination with retinal laser treatment and intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy in case complications of the disease occur [14–16]. However, the watch-and-wait approach has drawbacks, including the need for frequent visits and the risk of progression in the interim, which causes high levels of uncertainty for patients. Furthermore, some patients do not have a complete response to photocoagulation and anti-VEGF treatments [17], and the burden associated with receiving intravitreal therapy (IVT) can lead to treatment noncompliance [18, 19]. Given the burden to the patient associated with current treatment strategies and the fact that the visual impairment associated with DR can profoundly impact patients' quality of life [19], the patient experience is vital to include in research evaluating novel therapies [20].

In the present study, we explore the findings of a simulation involving patients and study site staff of a phase II clinical trial in nonproliferative diabetic retinopathy (NPDR). The aim of the sham-controlled phase II clinical trial that was simulated was to assess the efficacy and safety of IVT injection of a novel monoclonal antibody in patients with NPDR [21–23]. The aim of the simulation was to better understand patient, HCP, and other study site staff views on: appropriate patient eligibility criteria, challenges around IVT in trials, participant goals for the trial, and barriers to participation.

METHODS

Simulation Study Design

The study was conducted between March 27 and May 31, 2023, with participants including people living with NPDR and site staff (investigators or nurses/coordinators) from the USA, United Kingdom (UK), and Germany.

Participants were recruited and contracted through Good Market Research Practices. They then took part in the trial simulation (see details below) before attending a web-assisted

telephone interview to provide feedback on the trial design and material presented during the simulation. A group from the study, comprising two site staff experts and one patient expert, convened to discuss the insights generated and advise on actions that could be taken to optimize the clinical trial design.

Ethics Statement

Market research does not require Institutional Review Board (IRB) approval because it falls outside the remit of the governance arrangements for research ethics committees. The market research conducted was carried out to understand behavior and opportunities and inform business decision-making. The project was conducted in line with local data protection laws and Market Research Society's Code of Conduct, including British Healthcare Business Intelligence Association, European Society for Opinion and Market Research, European Pharmaceutical Market Research Association, and other relevant national codes of practice. No clinical assessments were undertaken as part of the project which would then necessitate IRB approval. The participants were selected independently of the sponsor and consented to participating in the market research project in line with standard market research guidelines.

Simulation Study Participants

Eligibility criteria for people with NPDR included that they must have been diagnosed with moderate, moderately severe, or severe NPDR by an ophthalmologist; there must have been a mix of experiences with prior eye injections among the group; and the group must have included participants who had, and those who had not, considered participating in clinical trials.

Site staff were eligible for the study if they were an investigator or nurse coordinator specializing in ophthalmology or had a focus in retinal health, had a minimum of 2 years' experience as a clinical trial investigator or nurse coordinator, and had been previously involved in at least five ophthalmology clinical trials.

Simulation

Participants were asked to spend 30 min reviewing a preread and an animation of the trial design [24] (Fig. 1), which had a simple layout and a voiceover to make the content appropriate to people with potential visual impairment. Key aspects of the clinical trial that were simulated included the study objective, endpoints, patient population, study duration, and visit frequency (Fig. 1).

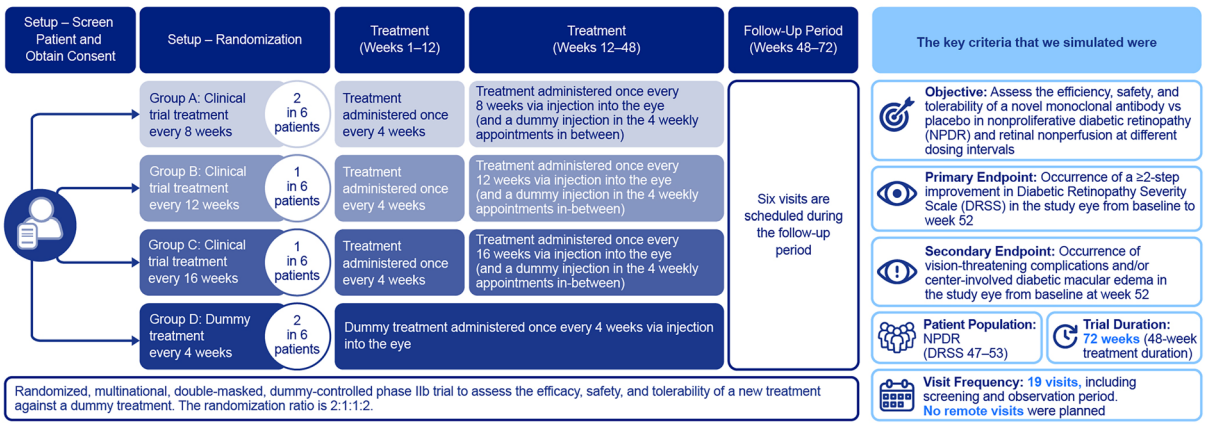

Fig. 1 Key trial design details included in the simulation

Interviews

Following the simulation, participants took part in a 75–90-min web-assisted telephone interview. Interviews took place from March 27 to May 31, 2023.

Four show cards were presented to participants during the interview to remind them of the trial content. Moderators followed set questions, with timed use of the show cards indicated for certain questions. Questions asked in the interview varied based on participant identity (people with NPDR vs. HCP/site staff) and location (USA, UK, Germany). The questions were designed to gather overall feedback on the trial design, as well as to elicit more in-depth feedback on certain aspects, including recruitment (site staff only); the inclusion/exclusion criteria; treatment and randomization; endpoints; duration, visit schedule, and assessments; and follow-up. Example questions and show card contents are provided in the supplementary material (Appendices A–D), as are the trial eligibility criteria (Appendix E).

Patient participants were asked to rank their likelihood of participating in the simulated clinical trial on a Likert scale from 1 to 7 (1 being not interested at all; 7 being extremely interested). Site staff participants were asked to describe how challenging it would be to run the simulated clinical trial out of their particular study site, again using a Likert scale from 1 to 7 (1 being "not challenging at all"; 7 being "extremely challenging").

Participant Advisory Panel

There were two interim debriefs that were attended by a small panel consisting of two expert site staff and one patient expert. During these debriefs, the group listened to the interviews and were given a summary of the findings to assist in the discussion. They then provided preliminary recommendations based on what was presented. These advisors also met following the conclusion of the interviews to interpret the overall data and cocreate potential trial solutions.

Analysis

Responses were analyzed thematically, and participant demographics and characteristics were summarized via descriptive statistics. Recordings and transcripts of the interviews, as well as finding summaries, were analyzed and discussed by the panel of experts. The three-person expert panel, in conjunction with the trial design team, identified the main challenges with the trial design. They ranked the challenges based on which had the most potential impact on the patient experience of the trial, to prioritize solution implementation.

RESULTS

Simulation Participant Characteristics

Overall, 22 patients living with different severity levels of NPDR (Table 1) and 16 site staff members participated in the simulation (Table 2).

Most patients living with NPDR who participated fell within the age range of 36–55 years and were mostly white (18/22; 81.8%) and female (13/22; 59.1%). Many (13/22; 59.1%) had not considered taking part in an NPDR clinical trial before. No patients had previously participated in an NPDR clinical trial, although 4/22 (18.2%) reported participating in non-NPDR clinical trials. There was a mix of NPDR severity, with 5/22 (22.7%) having moderate, 11/22 (50.0%) having moderately severe, and 6/22 (27.3%) having severe NPDR. Overall, 12/22 (54.5%) of participants reported having prior IVT experience.

Site staff had a mean of 12 years' experience and had completed a mean of 7.5 diabetic retinopathy clinical trials previously. There was an equal number of NPDR site investigators and site coordinators/nurses (eight of each). They came from a mix of settings with eight (50.0%) from university teaching hospitals or regional equivalents, seven (43.8%) from private practice, and one (6.3%) from a district general hospital.

Table 1 Demographics and characteristics of people living with nonproliferative diabetic retinopathy (NPDR) who participated in the simulation

Patient demographics and characteristics	US-based ($n = 8$)	UK-based ($n = 8$)	Germany-based ($n = 6$)	Overall ($N = 22$)
Mean age, years	49	35	53	45
Women, *n* (%)	5 (62.5)	5 (62.5)	3 (50)	13 (59.1)
Race, *n* (%)				
White	6 (75.0)	6 (75.0)	6 (100)	18 (81.8)
Black	1 (12.5)	1 (12.5)	0 (0)	2 (9.1)
Asian	0 (0)	1 (12.5)	0 (0)	1 (4.5)
Multiple	1 (12.5)	0 (0)	0 (0)	1 (4.5)
Education level				
Master's degree or above	3 (37.5)	3 (37.5)	1 (16.7)	7 (31.8)
Bachelor's degree	2 (25.0)	1 (12.5)	1 (16.7)	4 (18.2)
High school or secondary school	3 (37.5)	1 (12.5)	3 (50.0)	7 (31.8)
Other	0 (0)	1 (12.5)	1 (16.7)	2 (9.1)
Prefer not to say	0 (0)	2 (25.0)	0 (0)	2 (9.1)
Mean duration since diagnosis, years	13	10	5	9
NPDR severity, *n* (%)				
Moderate	3 (37.5)	2 (25.0)	0	5 (22.7)
Moderately severe	4 (50.0)	3 (37.5)	4 (66.7)	11 (50.0)
Severe	1 (12.5)	3 (37.5)	2 (33.3)	6 (27.3)
Ocular comorbidities, *n* (%)				
Diabetic macular edema	1 (12.5)	2 (25.0)	1 (16.7)	4 (18.2)
Glaucoma	0	0	0	0
Cataract	1 (12.5)	1 (12.5)	0	2 (9.1)
Diabetes type, *n* (%)				
Type 1 diabetes mellitus	2 (25.0)	3 (37.5)	2 (33.3)	7 (31.8)
Type 2 diabetes mellitus	1 (12.5)	0	0	1 (4.5)
Not reported	5 (62.5)	5 (62.5)	4 (66.7)	14 (63.6)
Prior intravitreal therapy experience, *n* (%)				
Yes	5 (62.5)	4 (50.0)	2 (33.3)	11 (50.0)
No/missing	3 (37.5)	4 (50.0)	4 (66.7)	11 (50.0)

Table 1 continued

Patient demographics and characteristics	US-based ($n=8$)	UK-based ($n=8$)	Germany-based ($n=6$)	Overall ($N=22$)
Prior clinical trial participation (NPDR and non-NPDR), *n* (%)				
Yes	0	2 (25.0)	2 (33.3)	4 (18.2)
NPDR trial	–	0	0	0
No	8 (100)	6 (75.0)	4 (66.7)	18 (81.8)
If yes, positive experience with prior trial reported	–	2 (100)	2 (100)	4 (100)

Table 2 Characteristics of site staff who participated in the simulation

Site staff characteristics	US-based ($n=6$)	UK-based ($n=6$)	Germany-based ($n=4$)	Overall ($N=16$)
Site staff type, *n* (%)				
Nonproliferative diabetic retinopathy (NPDR) site investigator	3 (50.0)	3 (50.0)	2 (50.0)	8 (50.0)
NPDR site coordinator/nurse	3 (50.0)	3 (50.0)	2 (50.0)	8 (50.0)
Mean number of diabetic retinopathy trials completed, *n*	9.2	3.8	3.8	7.5
Site setting, *n* (%)				
University teaching hospitals or regional equivalents	0 (0)	4 (66.7)	4 (100)	8 (50.0)
Private practice	6 (100)	1 (16.7)	0 (0)	7 (43.8)
District general hospital	0 (0)	1 (16.7)	0 (0)	1 (6.3)

Note that some totals may exceed 100% due to rounding

Insights on Trial Inclusion/Exclusion Criteria Which May Impact Recruitment

Overall, the inclusion and exclusion criteria were considered similar to other trials, but instances where the criteria may present recruitment challenges were noted (Fig. 2).

Patients and site staff were concerned about the washout periods following prior treatments and trial participation (Fig. 2). Some patients worried about disease progression if they stopped treatment and would not stop treatment if their current therapy was working, while site staff anticipated patients' discomfort in this regard and said prolonged washouts would deter eligible patients, given the potential use of anti-VEGF in the population. Reducing the washout period following anti-VEGF treatment from 6 to 3 months was suggested as a solution. Exclusion of patients with macular edema was another concern, as its prevalence increases with increasing NPDR severity [25].

Multiple site staff said few patients would be eligible to participate if the eligibility criteria were followed; however, they provided

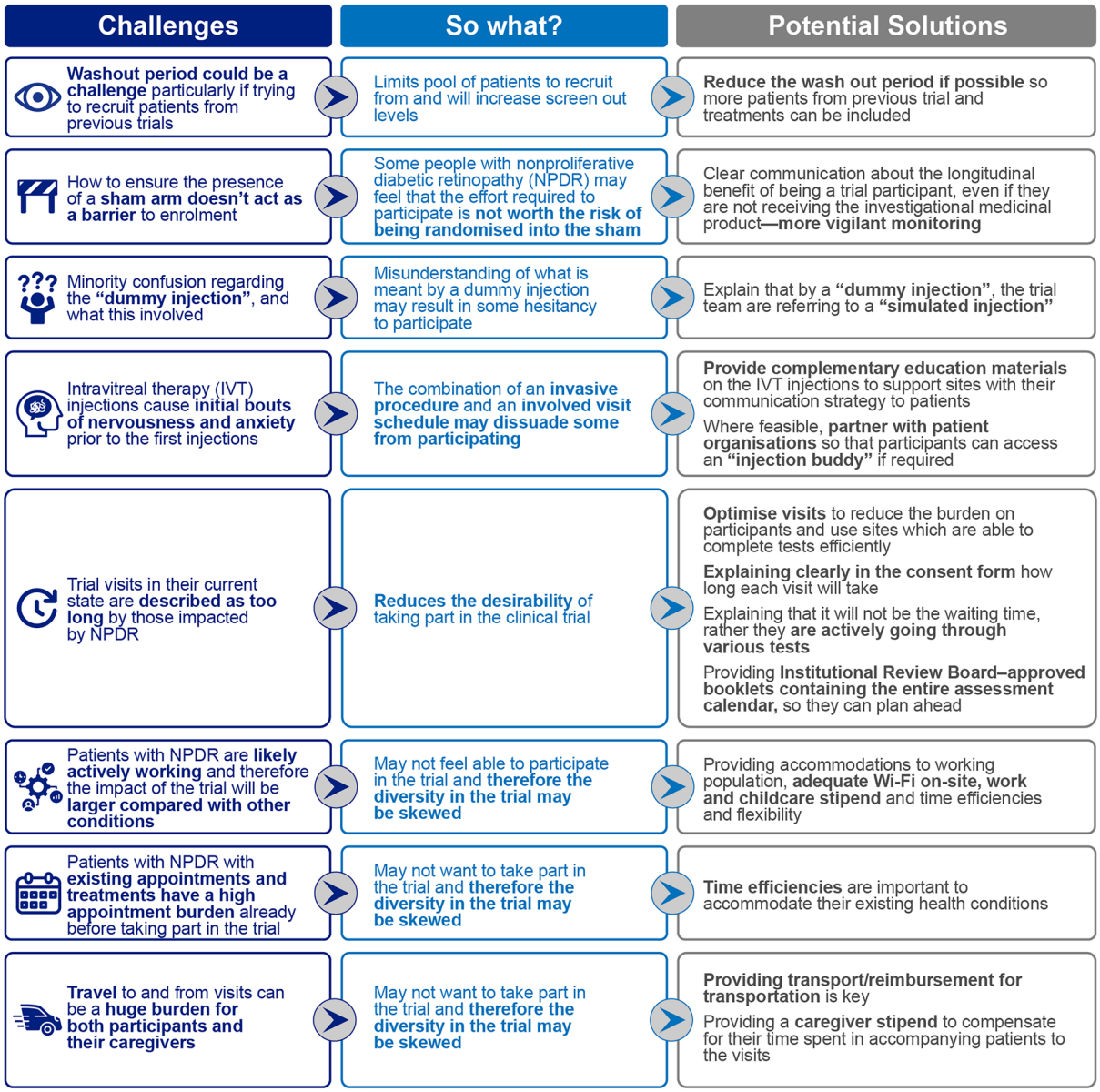

Fig. 2 Key identified challenges with the trial design, their implications for trial conduct, and potential solutions

suggestions for how recruitment challenges could be overcome and how patients could be encouraged to participate. Examples of this included connecting with diabetes centers to receive referrals for eligible patients, providing education on treatment risks and benefits (especially for asymptomatic patients), and highlighting the uniqueness of the trial and its endpoints and how these can benefit patients.

Insights on Trial Endpoints and Potential Impact on Participation

Site staff felt that the trial endpoints were standard but did not match patient goals. The proposed primary endpoint of Diabetic Retinopathy Severity Scale (DRSS) improvement is often used as an endpoint in DR trials, and site

staff expressed that patients' main interest is vision preservation, even for asymptomatic patients. As such, there was an expectation that best-corrected visual acuity would be the primary endpoint. They also expected to see other quality of life measures (e.g., visual disability score or visual function) included. Additionally, a minority of respondents queried the choice of DRSS as the primary endpoint due to its potential subjectivity and vulnerability to multiple interpretations. Site staff did express overall positive feeling toward change in nonperfusion index as a secondary endpoint, as this is not usually measured and was seen as a clinically important differentiator.

Regarding treatment goals, consistent with site staff responses, patients focused on saving vision, and primarily defined success as prolonging their ability to work, read, drive, look at a screen, and see in the dark. Other patient treatment success metrics/definitions were improvement of condition, bleeding cessation, decreased blurriness, and stabilization specifically for laser treatment eligibility.

Among German patients, neither stabilization of their condition nor slowing of deterioration was used to describe treatment goals more frequently than the other. Some geographic terminology differences emerged, with slowing of deterioration mentioned more frequently in the UK and stabilization used more frequently in the USA.

Insights on Trial Design

Overall, 36.4% of all patients felt the trial was not overly long, but half thought it was (13.6% were missing/nonresponders). However, patients generally understood the need for a trial of this length, and some noted that this duration of monitoring would be beneficial. Patients with comorbidities and/or an active work life expressed hesitancy due to the extra appointment burden for such a duration (Fig. 2). Ensuring the trial is well organized to allow participants to plan their time in advance could help mitigate these concerns.

Similarly, 45.5% of patients felt that a 4–5-h appointment time was acceptable, while 45.5% felt it was too long. The remaining patients did not respond or had missing responses. UK and German patients were more likely to report that the appointment time was too long (62.5% and 50.0%, respectively), while most US patients thought it was acceptable (62.5%). Some patients felt the "intense" schedule was problematic, as monthly visits are challenging for working participants with families and attendance at other diabetes appointments (Fig. 2).

For the 1:2 allocation ratio to sham or active treatment, 40.9% of patients with NPDR had a neutral attitude, 36.4% were positive, and 22.7% negative. Further questioning showed a 50% chance of randomization to a sham arm would be unacceptable for 27.3% of patients, and acceptable to only 13.6%, although there was a high proportion of neutral/nonresponses (59.1%). Some patients did not understand that the sham injection in an actual trial imitates the injection procedure rather than actually injecting anything (Fig. 2) and were concerned about the possibility of adverse events. For example, one person living with NPDR in the UK said, "When they said dummy treatment, are they going to put something? What will go into my eyes? I would like to know (…) is it (…) just a feeling of pressure and that's it? Is it that sort of thing that I will feel with the pain, but actually nothing has gone in?".

Site staff agreed that the trial duration would be a large commitment for patients and reported that a clear, simple explanation of the study design would make it acceptable to eligible participants. Trial design elements that the site staff identified as particularly important to communicate were clarification of the randomization ratio and a clear rationale for the sham arm. This included reasons for the sham, potential side effects, composition of the sham treatment, and reassurance that receiving sham treatment will not cause further deterioration. Site staff also identified the provision of reassurance that participants will be closely monitored and treated if DR progresses. They emphasized the importance of limited "waiting" time and organized progression through assessments and procedures and clarity on whether patients in the sham arm can receive treatment after the trial as necessary to communicate to patients.

Perspectives on Trial Treatment Administration

Patients reported fear or nervousness regarding IVT injections (Fig. 2), suggesting these fears need to be balanced with future vision loss risk. One summarized this by saying "I'd be lying if I wasn't a little nervous and scared. But if this is something that could prolong my health and help me and prolong my life, then I'll definitely do as much as I can and go as far as I can possibly go." Patients with no prior IVT injection experience were almost uniformly nervous/anxious about the concept (7/8 patients [87.5%] with responses); some patients with prior IVT injection experience also had negative views or expressed ongoing worries about it (5/9 [55.6%] with responses), but there were some (4/9 with responses [44.4%]) who said their nervousness had dissipated after the initial injection(s).

Some patients may not perceive a sufficiently great need for active intervention to warrant the discomfort, and many with earlier-stage DR believe lifestyle changes are enough to manage their condition. Approximately 50% of participants with prior IVT injection experience provided insights into strategies to improve the procedure experience. These included having adequate prior explanation of the procedure, anesthetic drops, a caring doctor to make the experience more pleasant, and aftercare, such as leaflets on how to keep the eye clean. They noted that materials should include information about the drug, the risks, IVT injection safety, eye clamping and drops, and aftercare. Additionally, the patient expert on the advisory panel suggested injection buddies could help those experiencing particularly high anxiety around IVT.

Site staff did not highlight the IVT injection as a major concern but did recognize that some participants who have not had these injections before may be anxious at the prospect. However, overall, it was thought that once the process and advantages are explained, most patients would be fine to proceed. Site staff also agreed with patients on potential interventions to make patients more comfortable, including having conversations explaining the procedure and risks thoroughly, and providing IVT educational materials.

Interest in Participating in the Trial

Overall, patients reported a mean interest score for trial participation of 4.9/7 (Fig. 3). Interest was highest in the US cohort (5.2/7) and lowest in the German cohort (3.3/7). Most site staff (62.5%) were also interested in conducting the trial (Fig. 3), with the highest interest reported in the German cohort (75.0%) and lowest interest reported the US cohort (50.0%).

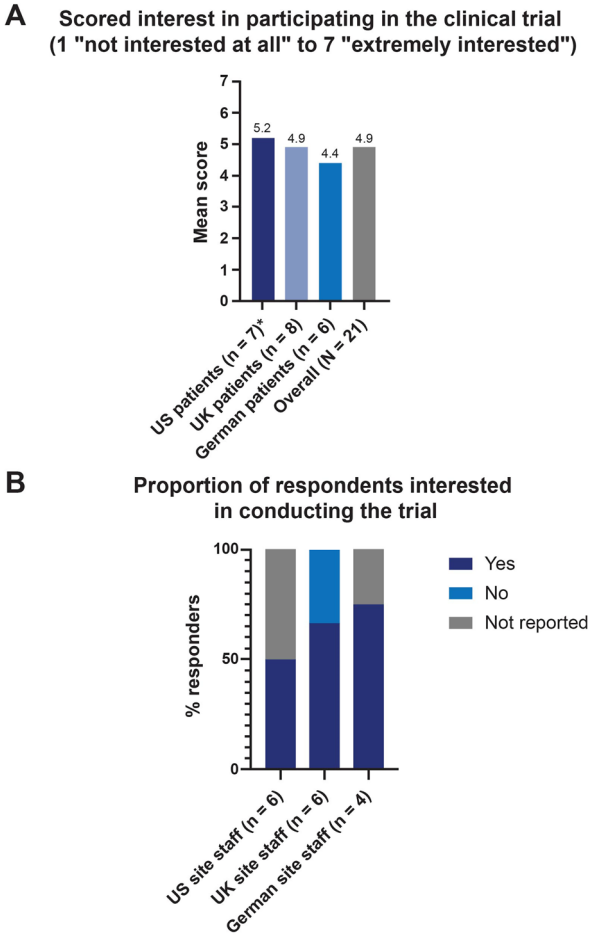

Fig. 3 Patient (*top*) and site staff (*bottom*) interest in participating in the clinical trial. *One US patient did not provide a response for this question

Trial Adaptations

The key challenges identified by participants, their implications for trial conduct, and potential solutions, including expert panel discussions, are summarized in Fig. 2. Patient and site staff feedback also precipitated specific actions in the trial patient and site engagement plan, such as offering patient and caregiver transportation and investigator training around close disease monitoring, as ways to help assuage patient concerns about the washout period.

Patient-centric education materials were also created as per the participants' suggestions; patient videos explained the procedures and rationale behind the study. Similarly, videos and websites specifically on the trial and indication were created and included with site and principal investigator training.

DISCUSSION

Overall, patients and site staff were generally interested in participating in a clinical trial such as the one described in the trial simulation. However, some key challenges to the conduct of the trial were identified by both patient and site staff respondents, particularly related to recruitment and retention of trial participants, with barriers including recruiting those with limited or no symptoms, potential for randomization to a sham injection arm, fears associated with IVT, and trial time commitment burdens. Respondents were generally aligned that adequate patient education regarding the benefits and risks of participation and detailed information regarding the trial conduct could help mitigate patient concerns and misperceptions. Ensuring that the trial is well organized and that scheduling difficulties are minimized could reduce participants' trial burden.

To our knowledge, this study is the first to include the collection of patient and site staff opinions on NPDR clinical trial design via a trial simulation. As such, our findings provide novel insights into challenges and barriers to participation in NPDR clinical trials. In addition, NPDR has many unique features compared with other ocular disease, such as diabetic macular edema and neovascular age-related macular degeneration (e.g., younger average patient age, lack of severe vision problems, more limited IVT experience and more trials with oral therapy alternatives, and the fact they may gain less direct treatment benefit or change in symptoms). These differences mean there is a particular value to studying the patient experience in NPDR prior to an IVT trial.

The benefits of incorporating the findings of studies such as these into future trial designs can be hard to quantify but are expected to include improved research quality and relevance and greater patient recruitment and retention [5]. As examples, a meta-analysis found a significant increase in enrollment in trials that engaged patients in the design process [26], while a modeling study found that the cost savings from improved enrollment, adherence, retention, and avoidance of one protocol amendment via the integration of patient engagement in trial design and conduct far outweigh the initial cost of the patient engagement activities [27]. The implementation of the patient experience into future NPDR trials would, therefore, be expected to foster patient centricity, improve recruitment, improve the overall patient experience in the trial, and enable the adaptation of assessments and endpoints to meet patients' needs. Given these considerations, application of the findings of this study to future NPDR clinical trials are likely to benefit both patients and researchers.

For adaptations to trial protocols based on insights gathered from patients and site staff, ideally, each participant's suggestion would be implemented, but expectations and goals pertaining to other functions, governance, physician advisory boards, and health authorities also needed to be considered. In cases where a participant's concern could not be accommodated, mitigation strategies would be implemented.

The importance placed by site staff on the choice of endpoints that are relevant to patients and the treatment goals identified by patients in this study is in line with previous studies, suggesting a link between DR severity and associated visual impairment with reduced mental health and poor psychosocial outcomes [28,

29]. Functional difficulties related to vision loss are prevalent in those with more severe NPDR, further demonstrating the importance of sight preservation [30].

Strengths of the study include the fact that respondents included both patients and site staff, providing insights from both main perspectives of trial conduct, and that the study also included respondents from three different countries, allowing for a greater diversity of opinions. Limitations of the study were the small number of participants and the thematic rather than robust statistical analysis of the results. In addition, despite increasing use of generative artificial intelligence in medical research for trial recruitment and retention, study designs, and trial conduct, it was not used in this study but would be of interest to explore in patient insight-based studies in the future.

CONCLUSIONS

In conclusion, the trial simulation provided valuable and novel insights into the challenges and barriers associated with trial design in NPDR. Key challenges included the need to stop existing treatments for 6 months prior to trial recruitment, fear of or nervousness towards IVT, and the burden associated with attending assessments and appointments. The potential solutions or increased awareness of these challenges suggested by respondents and the expert panel could be implemented with the aim of boosting NPDR trial recruitment, retention, quality, and the patient experience.

ACKNOWLEDGEMENTS

The authors would like to thank all patients and their caregivers who participated in this simulation study.

Authorship. The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and did not receive payment related to the development of this abstract. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy, as well as intellectual property considerations.

Author Contributions. Stela Vujosevic: Conceptualization, writing-review and editing, final draft approval. Ivana Gunderson: Conceptualization, writing-review and editing, final draft approval. Asma Burale: Conceptualization, writing-review and editing, final draft approval. Ben Moody: Conceptualization, writing-review and editing, final draft approval. Rebecca C. Stacy: Conceptualization, methodology, writing-review and editing, final draft approval. Martin Gliem: Conceptualization, methodology, writing-review and editing, final draft approval.

Funding. All authors have completed and submitted the ICMJE disclosures form. All authors have provided disclosure statements regarding financial interests or relationships, including those with none to disclose, which are provided prior to the references. The study was supported and funded by Boehringer Ingelheim. Medical writing and editorial assistance were provided by Abigail Killen-Devine, PhD, and Tabasum Mughal, PhD of Healthcare Consultancy Group (London, UK), with funding from Boehringer Ingelheim Pharma GmbH & Co. Boehringer Ingelheim also funded the journal's publication fee.

Data Availability. For publications reporting clinical study results, to ensure independent interpretation and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on "https://vivli.org/"- Center for Global Clinical Research Data, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Please

visit "https://www.mystudywindow.com/msw/datasharing" Medical & Clinical Trials | Clinical Research | "https://www.mystudywindow.com/msw/datasharing" MyStudyWindow for further information.

Declarations

Conflict of Interest. Stela Vujosevic: AbbVie, Inc., Alimera, Apellis Pharmaceuticals, Inc., Bayer, Boehringer Ingelheim, Novartis, RetinAI, Roche, Zeiss (consultancy fees). Ivana Gunderson: 4D Molecular Therapeutics, Inc., AbbVie, Inc., Alexion Pharmaceuticals, Inc., Annexon Biosciences, Apellis Pharmaceuticals, Inc., Boehringer Ingelheim Pharma GmbH & Co. KG., Cognition Therapeutics, Inc., Eyepoint Pharmaceuticals, Inc., F. Hoffman-La Roche Ltd, Genentech, Inc., IMA Group, Janssen Research & Development, LLC, Kyowa Kirin Co., Ltd., Stealth BioTherapeutics, Inc., The Lowy Medical Research Institute, Ltd, (financial support); Boehringer Ingelheim Pharma GmbH & Co. KG, F. Hoffman-La Roche Ltd, Ora, Inc (consultancy fees); Austin Clinical Research, LLC, Gunderson Research Consulting, LLC (personal financial interest). Asma Burale: Boehringer Ingelheim (consultancy fees). Ben Moody: None. Rebecca C. Stacy: Boehringer Ingelheim (employee). Martin Gliem: Boehringer Ingelheim International GmbH (employee).

Ethical Approval. Market research does not require Institutional Review Board (IRB) approval because it falls outside the remit of the governance arrangements for research ethics committees. The market research conducted was carried out to understand behavior and opportunities and inform business decision-making. The project was conducted in line with local data protection laws and Market Research Society's Code of Conduct, including British Healthcare Business Intelligence Association, European Society for Opinion and Market Research, European Pharmaceutical Market Research Association, and other relevant national codes of practice. No clinical assessments were undertaken as part of the project which would then necessitate IRB approval. The participants were selected independently of the sponsor and consented to participating in the market research project in line with standard market research guidelines.

REFERENCES

1. Qasim A, Devji T, Phillips MR, et al. Seeing the patient's perspective: a guide to patient-reported outcome measures and minimal important differences in ophthalmic research. Eye. 2022;36:1339–41. https://doi.org/10.1038/s41433-022-01989-5.

2. Dean S, Mathers JM, Calvert M, et al. "The patient is speaking": discovering the patient voice in ophthalmology. Br J Ophthalmol. 2017;101:700–8. https://doi.org/10.1136/bjophthalmol-2016-309955.

3. Murphy A, Bere N, Vamvakas S, Mavris M. The added value of patient engagement in early dialogue at EMA: scientific advice as a case study. Front Med (Lausanne). 2021;8:811855. https://doi.org/10.3389/fmed.2021.811855.

4. U.S. Food & Drug Administration. Patient-focused drug development: collecting comprehensive and representative input. 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input. Accessed 10 July 2024.

5. Faulkner SD, Somers F, Boudes M, Nafria B, Robinson P. Using patient perspectives to inform better

clinical trial design and conduct: current trends and future directions. Pharm Med. 2023;37:129–38. https://doi.org/10.1007/s40290-022-00458-4.

6. Hefele B, Langan SM, Pollins K, Gelfand JM. Engaging the patient's perspective in clinical trials research. J Investig Dermatol. 2019;139:1217–20. https://doi.org/10.1016/j.jid.2019.02.028.

7. Boisvert-Huneault C, Trigos Herraez D, Pinter A, et al. Understanding potential participation barriers to improve trial design and outcomes: clinical trial simulation in palmoplantar pustulosis as a case study. BMJ Open. 2023;13:e064159. https://doi.org/10.1136/bmjopen-2022-064159.

8. Jones S, Flewett M, Flewett R, et al. Clinical trial simulations in pulmonary fibrosis: patient-focused insights and adaptations. ERJ Open Res. 2023;9:00602-2022. https://doi.org/10.1183/23120541.00602-2022.

9. Lim SS, Kivitz AJ, McKinnell D, Pierson ME, O'Brien FS. Simulating clinical trial visits yields patient insights into study design and recruitment. Patient Prefer Adher. 2017;11:1295–307. https://doi.org/10.2147/PPA.S137416.

10. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376:124–36. https://doi.org/10.1016/S0140-6736(09)62124-3.

11. Kanavos P, van den Aardweg S, Schurer W. Diabetes expenditure, burden of disease and management in 5 EU countries. LSE Health, London School of Economics. 2012. http://www.lse.ac.uk/business-and-consultancy/consulting/assets/documents/diabetes-expenditure-burden-of-disease-and-management-in-5-eu-countries.pdf. Accessed 21 Aug 2024.

12. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5:e1221–34. https://doi.org/10.1016/S2214-109X(17)30393-5.

13. Leasher JL, Bourne RRA, Flaxman SR, et al. Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010. Diabetes Care. 2016;39:1643–9. https://doi.org/10.2337/dc15-2171.

14. Zhao M, Sun Y, Jiang Y. Anti-VEGF therapy is not a magic bullet for diabetic retinopathy. Eye. 2020;34:609–10. https://doi.org/10.1038/s41433-019-0652-3.

15. Lanzetta P, Loewenstein A. Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases. Graef Arch Clin Exp Ophthalmol. 2017;255:1259–73. https://doi.org/10.1007/s00417-017-3647-4.

16. Wong TY, Sun J, Kawasaki R, et al. Guidelines on diabetic eye care: The International Council of Ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology. 2018;125:1608–22. https://doi.org/10.1016/j.ophtha.2018.04.007.

17. Jenkins AJ, Joglekar MV, Hardikar AA, Keech AC, O'Neal DN, Januszewski AS. Biomarkers in diabetic retinopathy. Rev Diabet Stud. 2015;12:159–95. https://doi.org/10.1900/RDS.2015.12.159.

18. Segal O, Segal-Trivitz Y, Nemet AY, Cohen P, Geffen N, Mimouni M. Anxiety levels and perceived pain intensity during intravitreal injections. Acta Ophthalmol. 2016;94:203–4. https://doi.org/10.1111/aos.12802.

19. Sivaprasad S, Oyetunde S. Impact of injection therapy on retinal patients with diabetic macular edema or retinal vein occlusion. Clin Ophthalmol. 2016;10:939–46. https://doi.org/10.2147/opth.S100168.

20. Rofail D, Sherman S, Hartford C, et al. Development and preliminary validation of an instrument to measure symptoms and impacts in patients with proliferative diabetic retinopathy. Adv Ther. 2023;40:1773–86. https://doi.org/10.1007/s12325-023-02447-8.

21. Nguyen QD, Jhaveri C, Habib MS. Presented at: Association for Research in Vision and Ophthalmology; 2024. Oral presentation 959.

22. Boehringer Ingelheim. Phase 2. Indication: diabetic retinopathy (DR). 2024. https://www.boehringer-ingelheim.com/science/human-pharma/clinical-pipeline/retinal-health/bi-764524. Accessed 21 Aug 2024.

23. Boehringer Ingelheim. Boehringer Ingelheim shares positive results from the first study worldwide in diabetic macular ischemia. 2024. https://www.boehringer-ingelheim.com/science-innovation/human-health-innovation/positive-results-diabetic-macular-ischemia-treatment. Accessed 21 Aug 2024.

24. Boehringer Ingelheim. Video shown to patients taking part in the diabetic retinopathy trial simulation. 2025. https://doi.org/10.60915/Boehringer-figshare.29221040.v1. Accessed 05 June 2025.

25. Acan D, Calan M, Er D, et al. The prevalence and systemic risk factors of diabetic macular edema: a cross-sectional study from Turkey. BMC

Ophthalmol. 2018;18:91. https://doi.org/10.1186/s12886-018-0753-y.

26. Crocker JC, Ricci-Cabello I, Parker A, et al. Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. BMJ. 2018;363:k4738. https://doi.org/10.1136/bmj.k4738.

27. Levitan B, Getz K, Eisenstein EL, et al. Assessing the financial value of patient engagement: a quantitative approach from CTTI's patient groups and clinical trials project. Ther Innov Regul Sci. 2018;52:220–9. https://doi.org/10.1177/2168479017716715.

28. Khoo K, Man REK, Rees G, Gupta P, Lamoureux EL, Fenwick EK. The relationship between diabetic retinopathy and psychosocial functioning: a systematic review. Qual Life Res. 2019;28:2017–39. https://doi.org/10.1007/s11136-019-02165-1.

29. Valluru G, Costa A, Klawe J, Liu B, Deobhakta A, Ahmad S. Depression in individuals with diabetic retinopathy in the US National Health and Nutrition Examination Survey, 2005–2008. Am J Ophthalmol. 2023;256:63–9. https://doi.org/10.1016/j.ajo.2023.07.005.

30. Willis JR, Doan QV, Gleeson M, et al. Vision-related functional burden of diabetic retinopathy across severity levels in the United States. JAMA Ophthalmol. 2017;135:926–32. https://doi.org/10.1001/jamaophthalmol.2017.2553.